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Review

A comprehensive evaluation of single nucleotide polymorphisms associated with hepatocellular carcinoma risk in Asian populations: A systematic review and network meta-analysis

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ABSTRACT

Background: Single nucleotide polymorphisms (SNPs) have been inconsistently associated with hepatocellular carcinoma (HCC) risk. This meta-analysis aimed to synthesize relevant data on SNPs associated with HCC in the Asian population.

Methods: Databases were searched to identify association studies of SNPs and HCC in Asians published through January 2019. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on 41 studies (13,167 patients with HCC and 15,886 noncancer controls). Network meta-analysis and Thakkinstian's algorithm were used to select the most appropriate genetic model, along with false positive report probability (FPRP) for noteworthy associations.

Results: Eleven SNPs meeting the inclusion criteria were tested for association with HCC, including *CCND1* rs9344, *PTGS2* rs689466, *IL18* rs187238 and rs1946518, *KIF1B* rs17401966, *MDM2* rs2279744, *MIR146A* rs2910164, *MIR149* rs2292832, *MIR196A2* rs11614913, *MIR499A* rs3746444, and *TGFB1* rs1800469. A significant increase for HCC risk was observed for *MDM2* rs2279744, and the dominant (pooled OR = 1.59, 95% CI: 1.26–2.00) and codominant (pooled OR = 1.37, 95% CI: 1.18–1.60) models were determined to be the most appropriate models. *MIR499A* rs3746444 also showed a significant association with HCC risk under the allele contrast model (pooled OR = 1.36, 95% CI: 1.05–1.77). Only the significance of *MDM2* rs2279744 was noteworthy (FPRP < 0.2).

Conclusions: *MDM2* rs2279744 is associated with HCC susceptibility in Asians, and the dominant and codominant models are likely the most appropriate models to estimate HCC risk.

1. Introduction

Hepatocellular carcinoma (HCC), which accounts for 75–90% of primary liver cancer, is the third most common cause of cancer-related deaths worldwide (Bray et al., 2018). HCCs show great geographic variation; more than 70% new HCCs have been diagnosed in Asia and patients in China alone have accounted for 55% of new HCCs occurring annually worldwide (McGlynn et al., 2015; Park et al., 2015; Zhu et al., 2016). Despite recent advances in early diagnosis and therapeutics, prognosis remains poor for patients with HCC, showing an overall

Abbreviations: SNPs, Single nucleotide polymorphisms; HCC, hepatocellular carcinoma; ORs, Summary odds ratios; CIs, confidence intervals; FPRP, false positive report probability; HBV, hepatitis B virus; HCV, hepatitis C virus; LD, linkage disequilibrium; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CNKI, China National Knowledge Infrastructure; AFP, alpha-fetoprotein; HWE, Hardy-Weinberg equilibrium; PSRF, potential scale reduction factor; SROC, summary receiver-operating characteristic; AUC, area under the curve; +LR, positive likelihood ratio; −LR, negative likelihood ratio; DOR, diagnostic odds ratio

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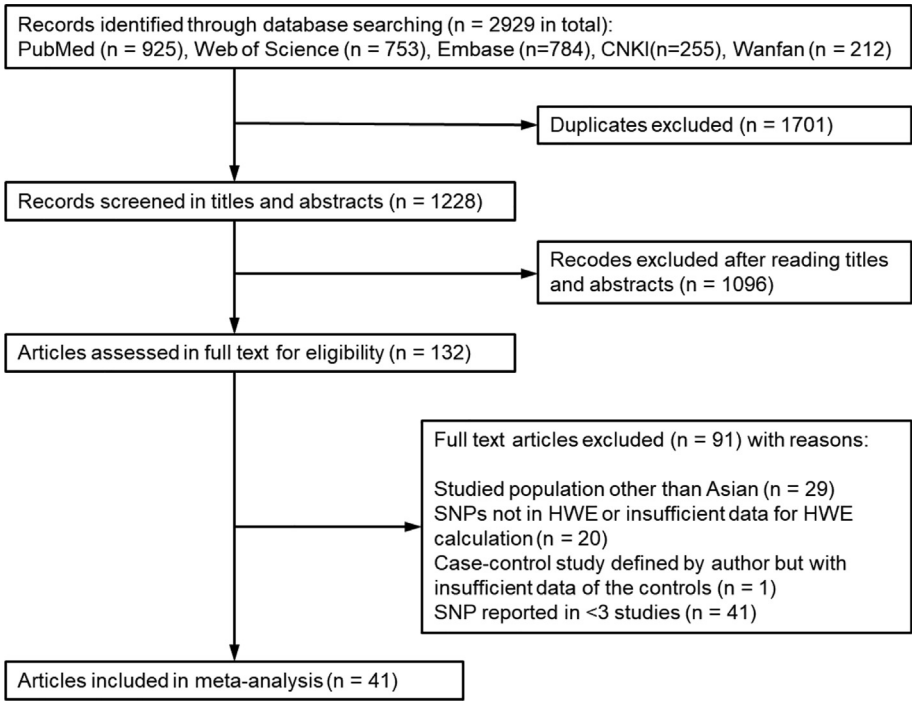

Fig. 1. PRISMA flow diagram of literature search and selection.

mortality-to-incidence ratio of 0.95 (Torre et al., 2015). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, dietary aflatoxin exposure, and chronic alcohol consumption are the major risk factors for developing HCC, but these leading risk factors show great geographic variation and differ by age and sex (Zhu et al., 2016; Leroy and Asselah, 2015; Liu and Wu, 2010). Individual genetic predisposition has also been proposed to contribute to HCC occurrence and geographic variation based on the findings in genetic association and familial aggregation studies (Dragani, 2010; Zhang et al., 2010). The fact that HCC is a complex disease involving multifactorial etiology and gene-environment interactions has resulted in research efforts to identify individuals susceptible to HCC.

Genetic variation is commonly represented by single nucleotide polymorphisms (SNPs), which are inherited single base changes in exonic or intronic regions. Although most SNPs are functionally neutral, some have been found to alter gene expression and function, or be in linkage disequilibrium (LD) with causal loci associated with cancer risk and/or prognosis. The past decades have witnessed burgeoning research on SNPs associated with HCC, and many gene SNPs derived from distinct pathways, such as tumor suppressors, inflammation, hepatic metabolism, DNA repair, and microRNA-mediated silencing, have been described to affect individual susceptibility to HCC (Laurent-Puig et al., 2001; Migita et al., 2007; Kim et al., 2012; Qiu et al., 2016; Long et al., 2010; Silvestri et al., 2003). Most of these studies, however, have limited statistical power to detect small-effect SNPs and the results are often inconsistent and thus inconclusive. Building upon these studies, systematic reviews have evaluated the evidence regarding SNPs in individual genes or signaling pathways related to HCC (Trepo et al., 2014; Xu et al., 2013; Wang et al., 2018), but few reviews have comprehensively summarized and evaluated all SNPs related to HCC.

The objective of this study was to comprehensively evaluate significant SNPs associated with HCC susceptibility in Asian populations. There is a lack of evidence to indicate which genetic model is most appropriate to identify associations of SNPs with HCC; thus, instead of assuming the underlying genetic model, we applied various approaches to select the most appropriate genetic models of inherence and to measure the reliability of the associations.

2. Materials and methods

This study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the protocol was registered in the PROSPERO database (CRD42019122135).

2.1. Search strategy and selection criteria

Studies published through January 2019 that compared frequency differences in SNPs between HCC patients and noncancer controls were identified from PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases, with no language limits. The search strategy was based on the following search terms: “single nucleotide polymorphism”, “SNP”, “hepatocellular carcinoma”, and “liver cancer”. Details regarding the search terms are available in the Supplementary Materials.

The following criteria were applied for study selection. Studies included case-control designs comprising HCC cases and noncancer controls. Cases had a primary diagnosis of HCC that was confirmed by histopathological examination or imaging features along with serum alpha-fetoprotein (AFP) levels. Studies were excluded if the diagnosis was based on criteria not aforementioned or diagnosis criteria were not clearly defined. Noncancer controls may be healthy or have non-malignant diseases, including hepatitis and cirrhosis. Studies were considered only if the studied population was Asian and cancer risk was the outcome. No restrictions were placed on age, gender, country, or tumor stage. A study was excluded if it was a repeat report, conference report, thesis, review paper, or animal study, or had insufficient data for genotyping distribution calculation. Studies in which SNPs demonstrated a departure from Hardy-Weinberg equilibrium (HWE) in controls were excluded. A SNP was included only if more than two studies meeting the aforementioned criteria evaluated this genetic variant. The references of all eligible studies were manually screened to ensure that all relevant studies were included.

2.2. Selection of studies, data extraction, and qualitative evaluation

Two reviewers (CZ and ZY) conducted the selection process independently, with cases of disagreement resolved by discussion or consulting a third reviewer (ZZ). Fig. 1 is the PRISMA flow diagram illustrating the procedure of study selection. A total of 2929 records were identified from the databases. After removing duplicates, the titles and abstracts of 1228 publications were screened and 132 full-text papers were reviewed for eligibility. In cases where published genotyping data were inadequate, corresponding authors were contacted for data necessary for inclusion. Finally, 41 papers meeting the selection criteria were included. Data extracted from individual papers include: author, year of publication, country, sample size, type of controls, sex composition, age of diagnosis, hepatitis types, and details of target SNPs, including genotyping methods, frequencies of genotypes and derivation from HWE.

The methodological quality of data was assessed based on the STREGA statement (Little et al., 2009). The following questions were rated using a two-point scale (0/no, 1/yes): (1) is there description of genotyping methods? (2) is there population stratification assessment? (3) is there description of methods for inferring genotypes? (4) is there description whether HWE holds in controls? (5) is there description of whether the study is the first report or a replication effort, or both? (6) is information given on eligibility criteria and matching criteria for matched case-control studies? (7) is there description of statistical methods and software version used? (8) is there description to address and correct for relatedness among subjects? and (9) is the data adequate? Two reviewers conducted the rating independently and a third reviewer was consulted for consensus if disagreement occurred.

2.3. Statistical analysis

For controls of each study, HWE was estimated using the goodness-of-fit test. For pairwise meta-analysis, A fixed- or random-effects pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated, depending on degree of heterogeneity under six genetic models (allele contrast model, homozygous model, heterozygous model, dominant model, recessive model, and over-dominant model). Heterogeneity was quantified with the I^2 statistic and P value; a I^2 statistic $<$ 50% and a $P > 0.1$ indicated low heterogeneity between studies, in which case the fixed-effect model was employed. For significant SNPs with evidence of heterogeneity in meta-analysis, assessment of sources of heterogeneity was employed using subgroup analysis if sufficient data existed. Publication bias was assessed using the Begg's and Egger's tests.

A random-effects network meta-analysis within a Bayesian framework was conducted using the GeMTC software (v 0.14.3) (van Valkenhoef et al., 2012). Four parallel Markov chain Monte Carlo simulations were run for a 20,000-stimulation burn-in phase and an additional 50,000-stimulation phase. Convergence was satisfied with a potential scale reduction factor (PSRF) value of 1.0 as the cut-off value. Consistency, referring to agreement between direct and indirect comparisons in terms of effect estimates, was evaluated by comparing consistency model with inconsistency model in terms of standard deviation of the random effect. The inconsistency model was used when an obvious deviation was detected; otherwise, the consistency model was used. This Bayesian approach was used to rank the probability of each genetic model for risk assessment for HCC and corresponding rank probability plots were generated.

We further compared genetic models to select the most appropriate model using the algorithm by Thakkinstian et al (Thakkinstian et al., 2005). A SNP consists of a dominant allele (G) and a recessive allele (g). Pairwise differences of GG versus gg (D1), Gg versus gg (D2), and GG versus Gg (D3) were calculated as pooled OR_1, OR_2, and OR_3, respectively, along with 95% CIs, in the pairwise meta-analysis. The most appropriate genetic model was determined to be: recessive model if $OR_1 = OR_3 \neq 1$ and $OR_2 = 1$, dominant model if $OR_1 = OR_2 \neq 1$ and $OR_3 = 1$, a complete over-dominant model if $OR_2 = 1/OR_3 \neq 1$ and $OR_1 = 1$, or codominant model if $OR_1 > OR_2 > 1$ and $OR_1 > OR_3 > 1$ (or if $OR_1 < OR_2 < 1$, and $OR_1 < OR_3 < 1$).

To assess the noteworthiness of the normally significant SNPs under the most appropriate genetic model determined by network meta-analysis or Thakkinstian' algorithm, false positive report probability (FPRP) was calculated assuming three levels of prior probabilities (low: 0.1; moderate: 0.01; high: 0.001) and an OR of 1.5, as previously described (Wacholder et al., 2004; Lohmueller et al., 2003). Significant SNPs with a FPRP value $<$ 0.2 were considered noteworthy (Wacholder et al., 2004).

Diagnostic meta-analysis was conducted to determine sensitivity and specificity of SNPs in predicting HCC risk using the Meta-DiSc software (Zamora et al., 2006). The correlation between the pooled sensitivity and specificity was estimated using the summary receiver-operating characteristic (SROC) curve and its area under the curve (AUC); positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR) were calculated accordingly. Spearman correlation analysis was used to evaluate heterogeneity related to threshold effect.

Data were analyzed using STATA software, version 14.0 (StataCorp, College Station, USA) unless otherwise described. A P value $<$ 0.05 was taken as statistically significant.

3. Results

3.1. Description of included studies

A total of 41 studies (Zhang et al., 2010; Kim et al., 2012; Qiu et al., 2016; Hu et al., 2014; Zeng et al., 2015; Chang et al., 2012; Liu et al., 2010; Karra et al., 2015; Migita et al., 2009; Bao et al., 2015; Zhang et al., 2016; Zhu et al., 2007; Fan et al., 2011; Xu et al., 2008; Chen et al., 2012; Lau et al., 2016; Su et al., 2014; Sawai et al., 2012; Sopipong et al., 2013; Chen et al., 2013; Tomoda et al., 2012; Dharel et al., 2006; Yoon et al., 2008; Wang et al., 2012; Yang et al., 2013; Wang et al., 2013; Zhou et al., 2012; Zhang et al., 2013; Cong et al., 2014; Wang et al., 2014; Yan et al., 2015; Kou et al., 2014; Han et al., 2013; Qi et al., 2010, 2014; Li et al., 2015; Ma et al., 2015; Yang et al., 2012; Xin et al., 2012; Qi et al., 2009; Xiang et al., 2012) comprising 13,167 patients with HCC and 15,886 noncancer controls were considered eligible. Table 1 summarizes the characteristics of studies included in the meta-analysis. Among 158 SNPs within 101 genes with published allele frequency data, 11 SNPs in 10 genes were included in the analysis as meeting the selection criteria. Of the 41 studies, 3 involved *cyclin D1* (*CCND1*) rs9344, 4 involved *prostaglandin-endoperoxide synthase 2* (*PTGS2*) rs689466, 6 involved *interleukin 18* (*IL18*) rs187238 and rs1946518, 5 involved *kinesin family member 1B* (*KIF1B*) rs17401966, 8 involved MDM2 proto-oncogene (*MDM2*) rs2279744, 4 involved *microRNA 146a* (*MIR146A*) rs2910164, 4 involved *microRNA 149* (*MIR149*) rs2292832, 6 involved *microRNA 196a-2* (*MIR196A2*) rs11614913, 4 involved *microRNA 499a* (*MIR499A*) rs3746444, and 4 involved *transforming growth factor beta 1* (*TGFB1*) rs1800469. Supplementary Table S1 shows the results of methodological quality assessment.

3.2. Pairwise meta-analysis

Table 2 summarizes the results of HCC risk associated with the 11 SNPs under six genetic models. *MDM2* rs2279744 was significantly associated increased risk of HCC under all genetic models except the over-dominant model. For *MIR499A* rs3746444, the fixed-effect meta-analysis showed that the C allele conferred a significantly increased risk to HCC under the allele contrast model (pooled OR = 1.36, 95% CI: 1.05–1.77). No association with susceptibility to HCC was found for other SNPs.

There was significant heterogeneity across studies for *MDM2*

Table 1
Characteristics of studies included for meta-analysis.

First author, year of publication	Country	Studied SNPs	Genotyping method	Sample size (case/control)	P_{HWE} in controls
Hu et al. (2014)	China	*CCND1* rs9344	PCR	220/220	0.0574
Zeng et al. (2015)	China	*CCND1* rs9344	TaqMan real-time PCR	238/181	0.7816
Zhu et al. (2007)	China	*CCND1* rs9344	PCR-RFLP	225/428	0.0727
Fan et al. (2011)	China	*PTGS2* rs689466,	TaqMan real-time PCR	780/780	0.5228
Chang et al. (2012)	China	*PTGS2* rs689466	PCR-RFLP	298/300	0.5699
Xu et al. (2008)	China	*PTGS2* rs689466	PCR-RFLP	270/540	0.1383
Liu et al. (2010)	China	*PTGS2* rs689466	PCR-RFLP	210/210	0.6779
Karra et al. (2015)	India	*IL18* rs187238, *IL18* rs1946518	PCR-SSP	271/280	0.3195
Migita et al. (2009)	Japan	*IL18* rs187238, *IL18* rs1946518	PCR-RFLP	47/63	0.5309
Chen et al. (2012)	China	*IL18* rs187238, *IL18* rs1946518	PCR-SSP	228/300	0.1835
Bao et al. (2015)	China	*IL18* rs187238, *IL18* rs1946518	PCR-RFLP	153/165	0.5481
Zhang et al. (2016)	China	*IL18* rs187238, *IL18* rs1946518	PCR-LDR	109/127	0.1098
Lau et al. (2016)	China	*IL18* rs187238, *IL18* rs1946518	StepOnePlus real-time PCR	342/559	0.3701
Su et al. (2014)	China	*KIF1B* rs17401966, *MDM2* rs2279744	PCR	160/160	0.7115
Zhang et al. (2010)	China	*KIF1B* rs17401966	TaqMan real-time PCR	276/266	0.8059
Sawai et al. (2012)	Korea	*KIF1B* rs17401966	TaqMan real-time PCR	164/144	0.3251
Sopipong et al. (2013)	Thailand	*KIF1B* rs17401966	PCR	202/196	0.7647
Chen et al. (2013)	China	*KIF1B* rs17401966	TaqMan real-time PCR	503/772	0.6468
Tomoda et al. (2012)	Japan	*MDM2* rs2279744	PCR	258/199	0.6396
Dharel et al. (2006)	Japan	*MDM2* rs2279744	TaqMan real-time PCR	187/248	0.8824
Yoon et al. (2008)	Korea	*MDM2* rs2279744	PCR	287/297	0.0557
Qiu et al. (2016)	China	*MDM2* rs2279744	PCR-RFLP	985/992	0.8599
Wang et al. (2012)	China	*MDM2* rs2279744	PCR-RFLP	310/480	0.4070
Yang et al. (2013)	China	*MDM2* rs2279744	TaqMan real-time PCR	350/230	0.8914
Wang et al. (2013)	China	*MDM2* rs2279744	PCR	166/157	0.0698
Zhou et al. (2012)	China	*MIR146A* rs2910164, *MIR499* rs3746444	PCR-RFLP	186/483	0.0558
Kim et al. (2012)	Korea	*MIR146A* rs2910164, *MIR149* rs2292832, *MIR196A2* rs11614913	PCR-RFLP	127/201	0.1898
Zhang et al. (2013)	China	*MIR146A* rs2910164, *MIR196A2* rs11614913	MS-based MassArray	997/998	0.9106
Cong et al. (2014)	China	*MIR146A* rs2910164	PCR-RFLP	206/218	0.7232
Wang et al. (2014)	China	*MIR149* rs2292832	PCR-RFLP	152/304	0.6229
Yan et al. (2015)	China	*MIR149* rs2292832, *MIR499A* rs3746444	PCR-RFLP	274/328	0.4491
Kou et al. (2014)	China	*MIR149* rs2292832	PCR-RFLP	271/532	0.8771
Han et al. (2013)	China	*MIR196A2* rs11614913	PCR	1017/1099	0.3103
Qi et al. (2010)	China	*MIR196A2* rs11614913	PCR-LDR	361/391	0.8691
Qi et al. (2014)	China	*MIR196A2* rs11614913, *MIR499A* rs3746444	PCR	314/406	0.1559
Xiang et al. (2012)	China	*MIR499A* rs3746444	PCR-RFLP	100/100	0.5633
Li et al. (2015)	China	*MIR196A2* rs11614913	PCR-RFLP	266/266	0.6887
Ma et al. (2015)	China	*TGFB1* rs1800469	PCR	159/234	0.1372
Yang et al. (2012)	China	*TGFB1* rs1800469	TaqMan real-time PCR	772/852	0.4409
Xin et al. (2012)	China	*TGFB1* rs1800469	TaqMan real-time PCR	347/881	0.5828
Qi et al. (2009)	China	*TGFB1* rs1800469	PCR-RFLP	379/299	0.2573

rs2279744 under the allele contrast, homozygous, dominant, and recessive models (Table 2). We explored the sources of heterogeneity using subgroup analysis and found that the heterogenicity was partially explained by differences in HBV/HCV status and country (Supplementary Table S2). Similar among all genetic models, the significant association between *MDM2* rs2279744 and HCC was more pronounced in HCV than HBV infected individuals, and in studies conducted in non-Chinese Asian compared to Chinese populations.

3.3. Determination of the most appropriate genetic models

To choose the most appropriate genetic model in HCC risk estimation, network meta-analysis under consistency model was performed to compare different genetic models of *MDM2* rs2279744 (Fig. 2). Convergence was reached for all analyses (data not shown). For *MDM2* rs2279744, the dominant model was superior to other genetic models; the differences were significant ($P < 0.05$ compared to any other models, Fig. 2). Rank probability indicated that HCC risk estimation was from best to worst: dominant, homozygous, allele contrast, heterozygous, and recessive model.

Thakkinstian's criteria were also used to select the most appropriate genetic model. For *MDM2* rs2279744, the codominant model was the best with the OR_1, OR_2, and OR_3, being 1.88 (95% CI, 1.40–2.52), 1.40 (95% CI, 1.16–1.69), and 1.26 (95% CI, 1.11–1.43), respectively. For *MIR499A* rs3746444, the results suggested that the genetic model was most likely to be codominant, based on the pooled OR_1, OR_2, and OR_3 of 1.52 (95% CI, 0.79–2.93), 1.36 (95% CI, 1.03–1.79), and 0.12 (95% CI, 0.08–0.19), respectively.

For these significant SNPs, FPRP values under different prior probability scenarios were calculated and the results are shown in Table 3. For *MDM2* rs2279744, under both the dominant and codominant model, FPRP values were below 0.2, suggesting that the significant association of *MDM2* rs2279744 with HCC risk was not a false positive. The association between *MIR499A* rs3746444 and HCC risk was not noteworthy with the FPRP values above 0.2.

3.4. Diagnostic meta-analysis

Diagnostic meta-analysis was performed to determine the performance of *MDM2* rs2279744 for identifying HCC. Under both the codominant and dominant model, threshold effects were determined to be likely, with Spearman correlation coefficients being 0.86 ($P = 0.007$) and 0.60 ($P = 0.120$), respectively. As such, the random-effects model was applied to construct the SROC curves (Fig. 3). As illustrated in Fig. 3A, for *MDM2* rs2279744 under the codominant model, the AUC and Q-value of the SROC curve was 0.5502 (standard error [SE], 0.0110) and 0.5377 (SE, 0.0083), respectively. The summary DOR was 1.37 (95% CI, 1.18–1.60). The summary sensitivity, specificity, +LR,

Table 2
Pairwise meta-analysis of the selected SNPs in association with risk for hepatocellular carcinoma (HCC) in Asian populations.

	Sample size		Heterogeneity			
Genetic model	Case	Control	I^2	*P*	Model	OR (95% CI)
CCND1 rs9344	683	829				
A vs G			76.2%	0.015	Random	0.98 (0.72–1.33)
AA vs GG			78.0%	0.011	Random	0.96 (0.50–1.87)
AA vs AG			37.8%	0.201	Fixed	1.01 (0.79–1.29)
AA + AG vs GG			66.8%	0.049	Random	0.94 (0.59–1.49)
AA vs AG + GG			66.0%	0.053	Random	1.00 (0.67–1.49)
AG vs AA + GG			0.0%	0.939	Fixed	0.96 (0.78–1.18)
PTGS2 rs689466	1558	1830				
G vs A			67.1%	0.028	Random	0.86 (0.72–1.03)
GG vs AA			67.6%	0.026	Random	0.75 (0.52–1.08)
GG vs GA			10.5%	0.340	Fixed	0.92 (0.78–1.09)
GG + GA vs AA			66.3%	0.030	Random	0.81 (0.61–1.08)
GG vs GA + AA			44.7%	0.143	Fixed	0.90 (0.76–1.05)
GA vs GG + AA			11.6%	0.335	Fixed	0.97 (0.84–1.11)
IL18 rs187238	1150	1494				
G vs C			81.2%	< 0.001	Random	1.09 (0.74–1.56)
GG vs CC			0.0%	0.870	Fixed	1.01 (0.62–1.62)
GG vs GC			86.0%	< 0.001	Random	1.12 (0.66–1.90)
GG + GC vs CC			0.0%	0.968	Fixed	1.01 (0.63–1.63)
GG vs GC + CC			85.3%	< 0.001	Random	1.11 (0.68–1.82)
GC vs GG + CC			85.7%	< 0.001	Random	0.90 (0.54–1.51)
IL18 rs1946518	1150	1494				
C vs A			63.0%	0.019	Random	1.06 (0.88–1.29)
CC vs AA			64.0%	0.016	Random	1.12 (0.75–1.68)
CC vs CA			0.0%	0.617	Fixed	1.04 (0.85–1.27)
CC + CA vs AA			57.4%	0.038	Random	1.14 (0.85–1.52)
CC vs CA + AA			33.8%	0.183	Fixed	1.08 (0.90–1.30)
CA vs CC + AA			0.0%	0.893	Fixed	1.08 (0.92–1.26)
KIF1B rs17401966	1305	1538				
G vs A			84.6%	< 0.001	Random	0.93 (0.68–1.28)
GG vs AA			80.0%	< 0.001	Random	0.92 (0.47–1.80)
GG vs GA			64.3%	0.024	Random	1.10 (0.66–1.84)
GG + GA vs AA			74.6%	0.003	Random	0.88 (0.64–1.21)
GG vs GA + AA			76.5%	0.002	Random	0.99 (0.55–1.80)
GA vs GG + AA			0.0%	0.544	Fixed	0.86 (0.74–1.00)
MDM2 rs2279744	2703	2763				
G vs T			69.8%	0.002	Random	1.37 (1.18–1.60)*
GG vs TT			67.3%	0.003	Random	1.88 (1.40–2.53)*
GG vs GT			5.3%	0.390	Fixed	1.26 (1.11–1.43)*
GG + GT vs TT			60.6%	0.013	Random	1.59 (1.26–2.00)*
GG vs GT + TT			47.4%	0.065	Fixed	1.44 (1.21–1.71)*
GT vs GG + TT			0.0%	0.590	Fixed	0.98 (0.88–1.10)
MIR146A rs2910164	1516	1900				
G vs C			51.8%	0.101	Random	0.98 (0.83–1.15)
GG vs CC			43.1%	0.153	Fixed	1.04 (0.84–1.28)
GG vs GC			8.3%	0.351	Fixed	0.98 (0.81–1.18)
GG + GC vs CC			52.3%	0.098	Random	0.98 (0.75–1.28)
GG vs GC + CC			26.1%	0.255	Fixed	0.98 (0.82–1.18)
GC vs GG + CC			26.1%	0.255	Fixed	1.06 (0.93–1.22)
MIR149 rs2292832	823	1365				
C vs T			63.2%	0.043	Random	1.07 (0.86–1.33)
CC vs TT			52.8%	0.095	Random	1.08 (0.71–1.65)
CC vs CT			43.4%	0.151	Fixed	1.15 (0.93–1.41)
CC + CT vs TT			16.7%	0.308	Fixed	1.03 (0.83–1.28)
CC vs CT + TT			56.6%	0.075	Random	1.12 (0.82–1.55)
CT vs CC + TT			0.0%	0.492	Fixed	0.91 (0.77–1.09)
MIR196A2 rs11614913	3081	3268				
T vs C			73.7%	0.002	Random	1.00 (0.86–1.16)
TT vs CC			73.1%	0.002	Random	1.01 (0.74–1.37)
TT vs TC			68.5%	0.007	Random	0.91 (0.72–1.16)
TT + TC vs CC			69.8%	0.005	Random	1.06 (0.84–1.34)
TT vs TC + CC			72.8%	0.002	Random	0.94 (0.74–1.19)
TC vs TT + CC			62.6%	0.020	Random	1.12 (0.94–1.33)
MIR499A rs3746444	874	1317				
C vs T			44.1%	0.167	Fixed	1.36 (1.05–1.77)*
CC vs TT			0.0%	0.720	Fixed	1.52 (0.80–2.93)
CC vs CT			0.0%	0.509	Fixed	0.12 (0.08–0.19)
CC + CT vs TT			58.5%	0.090	Random	1.31 (0.96–1.78)
CC vs CT + TT			0.0%	0.669	Fixed	1.13 (0.70–1.81)
CT vs CC + TT			65.8%	0.054	Random	1.29 (0.91–1.83)
TGFB1 rs1800469	1657	2266				
C vs T			73.9%	0.009	Random	1.00 (0.82–1.21)

(*continued on next page*)

Table 2 (*continued*)

Genetic model	Sample size		Heterogeneity			
	Case	Control	I^2	*P*	Model	OR (95% CI)
CC vs TT			73.4%	0.010	Random	1.01 (0.69–1.49)
CC vs CT			22.5%	0.276	Fixed	0.97 (0.84–1.13)
CC + CT vs TT			62.4%	0.046	Random	1.01 (0.77–1.33)
CC vs CT + TT			59.5%	0.060	Random	1.00 (0.80–1.27)
CT vs CC + TT			0.0%	0.950	Fixed	1.05 (0.92–1.19)

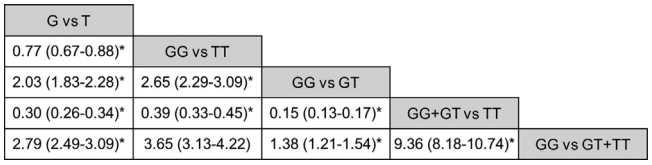

Fig. 2. League table of the results of network meta-analysis comparing genetic models of *MDM2* 309 rs2279744 in association with HCC risk, summarized with OR and 95% CIs. OR > 1 indicates that the top-left genetic model is better in terms of HCC risk assessment. *P < 0.05.

Table 3
False positive report probability (FPRP) for associations between the selected SNPs and hepatocellular carcinoma (HCC).

SNPs	OR (95% CI)	FPRP of different prior probability		
		0.1	0.01	0.001
MDM2 rs2279744[a]	1.37 (1.18–1.60)	0.00	0.00	0.04
MDM2 rs2279744[b]	1.59 (1.26–2.00)	0.00	0.03	0.22
MIR499A rs3746444	1.36 (1.05–1.77)	0.21	0.74	1.00

Abbreviations: FPRP, false positive report probability; OR, odds ratio; CI, confidence interval.
[a] co-dominant model.
[b] dominant model.

and −LR were 0.52 (95% CI, 0.51–0.53), 0.53 (95% CI, 0.52–0.55), 1.18 (95% CI, 1.08–1.28), and 0.86 (95% CI, 0.80–0.92), respectively. For *MDM2* rs2279744 under the dominant model (Fig. 3B), the AUC was 0.5502 (SE, 0.0171), with a Q-value of 0.5452 (SE, 0.0129). The summary DOR was 1.58 (95% CI, 1.26–2.00). The summary sensitivity, specificity, +LR, and -LR were 0.51 (95% CI, 0.50–0.53), 0.57 (95% CI, 0.54–0.60), 1.27 (95% CI, 1.11–1.46), and 0.81 (95% CI, 0.74–0.89), respectively.

4. Discussion

Several decades of intense research have generated large amounts of data on the genetic susceptibility of HCC, yet the empirical findings have been mixed and inconclusive regarding HCC susceptibility related to SNPs. In this study, we conducted a meta-analysis to combine findings from multiple studies and generate a more robust estimate of risk association to assess the current state of research on this topic. This is the first systematic review and meta-analysis to our knowledge to comprehensively assess SNPs associated with HCC among Asian populations. Our results revealed that, although *MDM2* rs2279744 and *MIR499A* rs3746444 were associated with HCC risk significantly in pairwise meta-analyses, only *MDM2* rs2279744 was noteworthy. The sensitivity and specificity of *MDM2* rs2279744 for predicting HCC risk were approximately 50–60%, which are close to the low end of the acceptable range of sensitivity and specificity. Therefore, *MDM2* rs2279744 alone is not feasible to screen for individuals at risk for HCC, but might be used as an adjuvant screening tool with other screening methods to improve HCC screening effectiveness. More studies are warranted to explore the possibility.

Risk association analysis based on a priori genetic model may be misleading if an inappropriate genetic model was assumed. Given that, in this study, no assumption was made, and in pairwise meta-analysis, genotypic significances of *MDM2* rs2279744 were observed under several genetic models. To identify the most appropriate model for HCC risk association, both network meta-analysis and Thakkinstian's algorithm were used. Network meta-analysis is an extension to pairwise meta-analysis and, similar to pairwise meta-analysis, its validity is based on quality of evidence. The ranking probability was obtained from a combination of direct and indirect evidence with a Bayesian approach. The use of network meta-analysis is becoming increasingly common for multiple comparisons in epidemiology (Elliott and Meyer, 2007; Hawkins et al., 2009), and while one study successfully applied this approach to select the best genetic model for detecting breast and ovarian cancer risk (Li et al., 2018), its feasibility and efficiency for genetic model comparisons remain to be tested in more studies. In this study, ranking results in network meta-analysis indicated that the dominant model of *MDM2* rs2279744 appeared to be superior to other genetic models for HCC risk association. However, the codominant model of *MDM2* rs2279744 was determined to be the best model based on Thakkinstian's criteria, a model-free approach achieving widespread use (Thakkinstian et al., 2005). This approach is based on observed magnitude of association without considering possible heterogeneity in

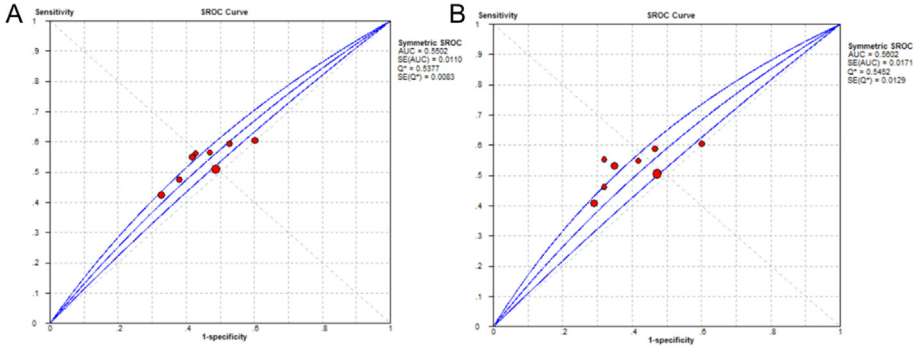

Fig. 3. Summary receiver-operating characteristic (SROC) curve of *MDM2* rs2279744 for identifying HCC under the (A) codominant and (B) dominant genetic models.

genetic effects that may occur due to confounding factors in studies. Low genotypic frequency in some genetic models may affect the power to detect phenotype association and distort the results. No prior studies have compared the efficiency of these two approaches for identifying the most appropriate genetic model; therefore, we present the results from both approaches. Moreover, subsequent FPRP analysis did not distinguish which genetic model was more noteworthy.

Our results showed that *MDM2* rs2279744 under both codominant and dominant models was significantly associated with HCC risk and the genetic association was unlikely to be a false positive according to FPRP analysis. MDM2 directly binds to p53 and negatively regulates its cellular localization, transcription activity, and proteasomal degradation (Momand et al., 1992; Haupt et al., 1997). *MDM2* rs2279744 (also known as SNP 309, T-to-G substitution), located in the first intron of MDM2, has been found to enhance the binding affinity toward the transcriptional activator Sp1 and consequently increase *MDM2* expression, leading to the attenuation of p53 pathway-mediated tumor suppression (Bond et al., 2004). The increased transcription of *MDM2* and reduced p53 activity caused by the G-allele of rs2279744 has been associated with accelerated tumor formation in cultured cell models (Bond et al., 2004; Hu et al., 2007) and increased risk for a wide variety of cancers in epidemiological studies (Yoon et al., 2008; Menin et al., 2006; Wasielewski et al., 2007; Bond et al., 2006). Notably, some evidence suggests that the increased risk of rs2279744 is gender-specific and estrogen-dependent in some cancers (Hu et al., 2007; Bond et al., 2006; Lind et al., 2006), whereas these patterns do not apply to all types of cancers and may be exclusive to specific racial and ethnic populations (Bittenbring et al., 2008; Park et al., 2006). Although remaining largely unknown, the gender-specific effect might contribute to the significant heterogenicity of *MDM2* rs2279744 across studies in this meta-analysis. Subgroup analysis indicated that the heterogenicity disappeared in HCV infected individuals and non-Chinese Asian populations, but was retained in the Chinese population. Chronic HBV infection is a major cause of HCC in Asian population, with the exception of Japan, where HCV infection is the major risk factor for HCC (Maucort-Boulch et al., 2018). Because of the small number of studies in non-Chinese Asians, we could not exclude the possibility that the subgroup differences in *MDM2* rs2279744 were due to chance. Regardless, the significance of *MDM2* rs2279744 for HCC risk was retained in all subgroups.

In this study the C-allele of *MIR499A* rs3746444 conferred a significantly increased risk for HCC under the allele contrast model in pairwise meta-analysis. Genetic model assessment based on Thakkinstian's algorithm revealed that the codominant model was the most appropriate model for risk analysis. The per-allele effect yielded in the allele contrast model was equal to the codominant model with HWE (Jin et al., 2011). Therefore, FPRP analysis for *MIR499A* rs3746444 under the allele contrast model was performed and the result indicated that the significance of association was not noteworthy. A previous meta-analysis did not detect a significant association between rs3746444 and HCC in Asians (Wang et al., 2016), but that analysis did not test the allele contrast model, which was the only model that detected a significant association in our pairwise meta-analysis. MicroRNAs are small non-coding RNAs that regulate gene expression in a wide variety of biological and pathological functions. Extensive research has demonstrated the regulatory effect of microRNAs in carcinogenesis (Lu et al., 2005; Croce, 2009). *MIR499A* rs3746444 (T-to-C transition), located in the stem region opposite to the mature *MIR499A*, has been suggested to affect expression of genes regulating cell growth and death, tumor invasion and metastasis, and immune response (Qiu et al., 2015). Overexpression of *MIR499* can suppress the expression of the proto-oncogene ETS1 in HepG2 cells, thereby promoting the degradation of extracellular matrix and playing a critical role in hepatocarcinogenesis (Wei et al., 2012). In addition, *MIR499A* demonstrated its anticancer property via antiangiogenic and direct tumor growth suppressive mechanisms (Ando et al., 2014). The expression of *MIR499A*-5p was found to be negatively correlated with PTEN; *MIR499A*-5p downregulation inhibited the PI3K/AKT/GSK signaling pathway and glycogen synthesis via targeting PTEN (Wang et al., 2015). Wang et al found that *MIR499A* inhibited cardiomyocyte apoptosis via suppressing the calcineurin-mediated dephosphorylation of dynamin-related protein-1 (Drp1) and subsequently reducing accumulation of mitochondrial Drp1 and Drp1-mediated mitochondrial fission (Wang et al., 2011). The association between *MIR499A* rs3746444 and HCC risk in this study was solely based on epidemiological data. To explore functional dependencies, we searched the GEO and TargetScan databases and identified *FAM134B*, *RCL1*, *RNF180*, *NME5*, *NOL4*, *SPATA6L*, *KRT7*, *CXXC4*, *GREM1*, *C9*, *ABCA8*, *RGAG4*, *KLRC3*, *GRIK1*, *ESRRG*, *CPEB3*, *DNALI1*, *GPM6A*, and *GRAMD1C* as the target genes predicted to be regulated by *MIR499*A-3p (Supporting document S1). Future studies of these genes and their function will provide valuable insight into the role of *MIR499A* in HCC development. Given the limited number of studies available for meta-analysis, the effect of *MIR499A* rs3746444 on HCC need to be verified with additional large-scale studies.

Several limitations should be noted. First, this meta-analysis only included studies of Asian populations, so the results are not generalizable to other populations with different racial backgrounds. Second, there was considerable heterogeneity of the pooled results and subgroup analysis did not fully explain the heterogeneity, suggesting the potential influence of other confounding factors not examined in this study. The fact that most included studies did not collect detailed data on all established risk factors makes it impossible to perform pooled analysis stratified by all confounders. Third, several included studies were of low quality based on the STREGA quality score classification, which may limit the validity of the pooled results, but subgroup analysis indicated that this was not a major concern. Fourth, we could not rule out that some relevant studies were not included in the meta-analysis, and therefore, the SNPs selected for meta-analysis may not be comprehensive. Finally, due to the relatively small sample size in the pooled analysis for some SNPs, caution should be taken when interpreting the results.

5. Conclusions

In conclusion, our meta-analysis provides evidence supporting *MDM2* rs2279744 as a susceptibility factor for HCC occurrence in Asians. The dominant and codominant models with *MDM2* rs2279744 appear to be the appropriate models for detecting the risk association with HCC. More studies with large sample sizes, detailed data regarding established risk factors for HCC, and high quality are warranted to verify the findings of this study and further evaluate the effect of gene-gene and gene-environment interactions in determining HCC risk.

6. Date availability

The data supporting this meta-analysis are from previously reported studies and datasets, which have been cited. The processed data are available from the corresponding author upon request.

7. Funding statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2020.144365.

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